Tumors of the Nervous System and Pituitary Gland Associated With Atomic Bomb Radiation Exposure

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Background: **The risk of developing nervous system tumors following exposure to ionizing radiation is not well quantified. We characterized the incidence of nervous system tumors among atomic bomb survivors as a function of radiation dose.** ***Methods:*** **Tumors of the nervous system and pituitary gland diagnosed between 1958 and 1995 among 80 160 atomic bomb survivors were ascertained using the Hiroshima and Nagasaki tumor registries, medical records, and death certificates. Pathologists reviewed slides and medical records to provide histologic diagnoses. Poisson regression analyses were used to characterize radiation effects on tumor incidence, which are expressed as excess relative risk per sievert (ERR_{Sv}). All statistical tests were two-sided.** ***Results:*** **A statistically significant dose-related excess of nervous system tumors was observed in the cohort (ERR_{Sv} = 1.2, 95% confidence interval [CI] = 0.6 to 2.1). The highest ERR_{Sv} was seen for schwannoma (4.5, 95% CI = 1.9 to 9.2). The risk for all other nervous system tumors as a group is also statistically significantly elevated (ERR_{Sv} = 0.6, 95% CI = 0.1 to 1.3). Risk increases, although not statistically significant, were seen for meningiomas (ERR_{Sv} = 0.6, 95% CI = –0.01 to 1.8), gliomas (ERR_{Sv} = 0.6, 95% CI = –0.2 to 2.0), other nervous system tumors (ERR_{Sv} = 0.5, 95% CI = <–0.2 to 2.2), and pituitary tumors (ERR_{Sv} = 1.0, 95% CI = <–0.2 to 3.5). The dose–response relationships were linear. For nervous system tumors other than schwannoma, excess risks were higher for men than for women and for those exposed during childhood than for those exposed during adulthood.** ***Conclusions:*** **A statistically significant dose response was observed for all nervous system tumors combined and for schwannoma considered separately, indicating that exposure to even moderate doses (i.e., <1 Sv) of radiation is associated with an elevated incidence of nervous system tumors. [J Natl Cancer Inst 2002;94:1555–63]**

Tumors of the brain and other parts of the nervous system are a heterogeneous group of neoplasms *(1).* Many adult neuroepithelial tissue tumors—gliomas including astrocytomas—arise from the glial cells that surround and support neurons. The most common form of malignant tumor, glioblastoma multiforme, is an extremely aggressive and often fatal cancer *(2).* The most common forms of benign nervous system tumors are meningiomas and schwannomas (sometimes called neurilemomas). Meningiomas (tumors of the meninges) usually arise from arachnoidal cells, whereas schwannomas arise from Schwann cells in the peripheral nerves. Schwann cells are the peripheral nervous system analogues of glial cells. Less common among adults are malignant lymphomas of the central nervous system and germ cell tumors involving regions near the pineal and pituitary glands. Tumors of the pituitary and pineal glands are also intracranial tumors, but the epidemiology and etiology of these endocrine tumors are substantially different than those for nervous system tumors *(3,4).*

Although the etiology of nervous system tumors is not well described, several epidemiologic studies *(5–12)* have reported increased risks of meningiomas, nerve-sheath tumors, and gliomas after high-dose medical treatment, especially for those exposed during infancy or childhood. Less epidemiologic data are available regarding the risk of nervous system tumors for those exposed as adults. After reviewing five epidemiologic studies, Preston-Martin and White *(13)* concluded that increased risks of meningioma and schwannoma were associated with a history of diagnostic x-ray exposures (both dental and medical) performed many years ago when the level of radiation exposure may have been substantial. However, radiation associated with dental x-rays has not been related to an excess risk of nervous system tumors in other studies *(14,15).* Previous radiotherapy to the head has been related to excess risks of meningiomas and schwannomas *(16).* Information on glioma risks after low-dose radiation exposure or exposure as an adult is limited. Mortality studies *(17–19)* of workers exposed to low radiation doses did not find statistically significant effects, but mortality data are a poor measure of risk for nervous system tumors with relatively good survival, such as meningiomas and schwannomas.

Using data for the period from 1961 through 1975, Seyama et al. *(20)* reported a fivefold increase in brain tumor incidence among male atomic bomb survivors exposed to radiation levels of 1 Gy or more. In the most recent general analysis of Life Span Study (LSS) cancer incidence data *(21),* an increased risk of extracranial neural tissue tumors was suggested, but there was little evidence of a radiation-associated increase in brain tumor risk. More recently, increased risks of meningioma associated with atomic bomb radiation exposure or distance from the bombs were reported in Hiroshima *(22)* and in Nagasaki *(23).*

To further understand the role of radiation in the etiology of brain and other neural tumors, we conducted a detailed incidence study, including a pathology review, in the LSS cohort of atomic bomb survivors. Specifically, we examined the dose–response

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relationship, quantified radiation risks for specific histologic types of malignant and benign tumors, and evaluated the role of modifying factors on the dose response.

Materials and Methods

Radiation Terminology

Gy (gray units) are used to refer to doses of radiation in which no allowance is made for the biologic effectiveness of different types of radiation. If allowance is made for the different effectiveness of various types of radiation, then the resulting dose equivalent is expressed using sieverts (Sv). An absorbed dose of 1 Gy is equal to 100 rad, and 1 Sv is equal to 100 rem. A given dose of neutrons is believed to have greater biologic effectiveness than the same dose of γ-rays or x-rays.

Life Span Study Population

Case ascertainment was carried out for the full LSS cohort, which includes 93 000 atomic bomb survivors from Hiroshima and Nagasaki and 27 000 people who were not in the cities at the time of exposure. The population used in these analyses includes 80 160 members of the LSS cohort for whom organ dose estimates can be computed, who were in Hiroshima or Nagasaki at the time of the atomic bombings, and who were alive and not known to have had cancer at the time of the establishment of the Hiroshima and Nagasaki Tumor Registries (January 1958). The population differs from that described in *(21)* because of the inclusion of 234 people with dose estimates of 4 Gy or more and the exclusion of 46 people on the basis of new follow-up data. At the end of follow-up, in December 1995, slightly more than 50% of the cohort members were still alive. There are more women (60%) than men in the cohort (Table 1), particularly in the group of people who were 20–39 years old at the time of the atomic bombings. Almost 68% of the study group was exposed to radiation from the bomb in Hiroshima. Individual weighted brain doses were calculated as the sum of the γ-ray dose plus 10 times the neutron dose by using the DS86 system *(24,25).* Weighted dose was used to allow for the greater biologic effectiveness of neutron radiation doses. The dose estimates incorporate a correction for bias arising as a result of random errors in individual dose estimates *(26).* Approximately 40% of the cohort had a weighted brain dose of less than 0.005 Sv. Only 2811 survivors (3.5%) had dose estimates greater than 1 Sv. Mabuchi et al. *(27)* and Thompson et al. *(21)* have described the characteristics of the LSS cohort in detail.

Tumor Ascertainment

Tumors of the brain, cranial and spinal nerves, pituitary gland, and pineal gland were ascertained through the population-based Hiroshima and Nagasaki Tumor Registries, which were established in 1958 *(27).* To improve ascertainment for benign tumors, the tumor registry data were augmented with informa-

Table 1. Selected characteristics of atomic bomb survivors in the Life Span Study: cancer incidence follow-up, 1958–1995

	No. of subjects with nervous system tumors*	No. of subjects with pituitary tumors*	Total No. of subjects	Person-years†
Sex				
Female	150	19	47 755	1 244 140
Male	78	16	32 405	745 157
City of exposure				
Hiroshima	171	28	54 153	1 376 381
Nagasaki	57	7	26 007	612 916
Clinical cohort membership‡				
Yes	68	7	14 325	366 500
No	160	28	65 835	1 622 797
Age at exposure, y				
0–9	36	5	17 681	483 820
10–19	49	11	17 180	491 553
20–39	68	7	22 369	645 557
⩾40	75	12	22 930	358 367
Attained age, y				
<35	5	4	—	361 520
35–49	44	9	—	529 660
50–64	80	8	—	599 261
65–79	73	11	—	400 106
⩾80	3	3	—	98 750
Weighted brain dose, Sv§				
<0.005	86	6	32 559	805 018
0.005–0.099	70	19	30 275	755 742
0.10–0.49	37	5	11 237	280 956
0.50–0.99	15	2	3 278	80 761
⩾1.00	20	3	2 811	66 820
Total	228	35	80 160	1 989 297

*First primary tumors only. — = not applicable.

†Migration-adjusted person-years.

‡The clinical cohort is a subset of the Life Span Study whose members were invited to participate in biennial medical examinations at the Radiation Effects Research Foundation.

§Weighted doses were used to allow for greater biologic effectiveness of neutron doses. Individual weighted brain doses were calculated as the sum of the γ-ray dose plus 10 times the neutron dose using the DS86 system *(24,25)* and are expressed in sieverts (Sv).

tion obtained from the Hiroshima and Nagasaki Tissue Registries (established in 1973); autopsy, surgical pathology, and clinical records from the Radiation Effects Research Foundation (RERF); and from major medical institutions in Hiroshima and Nagasaki.

A broad range of reported tumor diagnoses were considered in the initial stages of the ascertainment process. The 9th revision of the International Classification of Diseases (ICD-9) topography codes *(28)* considered in the initial screening were codes 191 (brain), 192 (other and unspecified parts of the nervous system), 194.3 (pituitary gland), 194.4 (pineal gland), 171.9 (connective tissue including peripheral and sympathetic nerves), 225 (benign neoplasms of brain and other parts of nervous system), 227.3 (benign pituitary gland neoplasms), 227.4 (benign pineal gland tumors), 237 (neoplasms of uncertain behavior of endocrine glands and nervous system), 239.6 (brain neoplasms of unspecified nature), and 239.7 (neoplasms of unspecified nature of endocrine glands and other parts of nervous system). The study pathologists also reviewed the records of tumors occurring in neighboring anatomic locations that might include misclassified neural tumors.

The four study pathologists (S. Yonehara, T. Kobuke, H. Fujii, and M. Kishikawa) independently reviewed pathology slides, pathology reports, and clinical records and classified tumors by anatomic site (topography), histologic type (morphology), and tumor behavior, according to World Health Organization (WHO) criteria *(29)*. When diagnoses differed, the pathology panel met to develop a consensus diagnosis.

Data Organization and Statistical Methods

Incidence for the various tumor types was cross-classified into 5-year age-at-exposure groups; 5-year attained-age groups; calendar time periods with an initial 3-year interval (from January 1, 1958, through December 31, 1960); and 5-year intervals for the period from January 1, 1961, through December 31, 1995; weighted brain dose estimates with cut points at 0, 0.005, 0.05, 0.1, 0.2, 0.5, 1, 2, 3, and 4 Sv; sex; city (Hiroshima or Nagasaki); and membership in the Adult Health Study (AHS) cohort *(30)*. Rates were computed with and without inclusion of tumors detected only at autopsy. Members of the AHS receive biennial clinical examinations at RERF and, therefore, the likelihood of early tumor detection is increased, particularly for tumors with only minor clinical symptoms. Autopsies were performed on large numbers of deceased members of the LSS in the course of a major autopsy program carried out between 1960 and the mid-1970s. Because benign and malignant tumors were a major focus of this program, the number of autopsies conducted could have influenced tumor incidence rates.

For each stratum, person-years, tumor counts, person-year-weighted average values for radiation exposure dose, attained age, age at radiation exposure, and time since exposure were computed. Person-years of observation were calculated from January 1, 1958, until the earliest of a) the date of diagnosis of the first primary tumor, b) the date of death or last known vital status, or c) the end of follow-up (December 31, 1995). Because of the completeness of the Japanese family registration system, less than 1% of the LSS cohort members have been lost to follow-up; about half the cohort members who were lost to follow-up could not be traced at the time the cohort was defined; the remaining half consisted of people who emigrated from Japan (emigration date is known). As with most previous studies of tumor incidence in the LSS [including *(21,31)*], we excluded tumors diagnosed outside the Hiroshima and Nagasaki tumor registry catchment area and adjusted the person-years on the basis of immigration and emigration information obtained from AHS cohort records *(21,32)*. This adjustment, which depends on city, sex, age, and time period, reduces the effective number of person-years by about 14%.

Imprecision in LSS survivor dose estimates results in an underestimation of radiation risk and some distortion in the shape of the radiation dose–response curve. To adjust for the impact of radiation dose errors, extremely large shielded body surface dose estimates were truncated to 4 Gy, and DS86 estimates were replaced with expected survivor dose estimates computed using the method developed by Pierce et al. *(26)* to produce bias-corrected risk estimates. These adjustments increase estimates of the slope of the dose response curve by about 10% in linear models.

Poisson regression methods *(33)* were used to compute maximum likelihood estimates for both excess relative risk (ERR) and excess absolute rate (EAR) models *(34)*. Parameter estimates, likelihood-ratio tests, and likelihood-based confidence intervals (CIs) *(33)* were computed with the AMFIT computer program *(34)*. We analyzed the data using general ERR models (the background rate times 1 plus the ERR) written as

$$\lambda(c,g,p,a,m)[1+\rho(d)\varepsilon(c,g,a,e,t,m)]$$

and general EAR models (the background rate plus the EAR) written as

$$\lambda(c,g,p,a,m)+\rho(d)\varepsilon^*(c,g,a,e,t,m)$$

In these models, $\lambda(\cdot)$ describes background nervous system tumor rates as a function of city (c), sex (g), time period (p), attained age (a), and membership in the AHS (m). These fitted background rates are estimates of the rates for an unexposed population. The function $\rho(\cdot)$ describes the dose–response shape. The functions $\varepsilon(\cdot)$ and $\varepsilon^*(\cdot)$ describe effect modification in the ERR and EAR models, respectively. Potential effect modifiers included the covariates c, g, a, and m, as well as age at exposure (e) and time since exposure (t). We generally present excess risk (ERR or EAR) estimates corresponding to specified values of any effect-modifying factors in the model. For example, if a model includes age at exposure or attained-age effects, we present the excess risk estimates at attained age 60 for a person exposed at age 30. The ERR, a dimensionless ratio, is positive if radiation increases risk, zero if there is no radiation effect, and negative when radiation exposure reduces risk. EARs have units of excess cases per 10 000 person-years per Sv and are positive when radiation increases tumor risk.

The log of the background rates was modeled as a sex-specific linear function of log-attained age with additional effects for time period and birth cohort. Categorical time period effects (1958–1971, 1972–1981, 1982–1995) were included to allow for the impact of the autopsy program. Neither city nor AHS membership had appreciable effects on the background rates. In some analyses, we excluded cases diagnosed only at autopsy. All P values are based on two-sided statistical tests.

Results

In this study, we examined the nature of radiation effects on nervous system tumor incidence in a large, fixed cohort of atomic bomb survivors. A total of 2655 tumors was screened to

identify primary nervous system, pituitary gland, and pineal gland tumors among cohort members. From this initial screening, 467 primary nervous system and pituitary gland tumors were identified. The consensus diagnoses were made on the basis of a review of pathologic specimens (including autopsy specimens) for almost 80% of the tumors, on clinical records for 10%, and solely on death certificate information for 10%.

Analyses were limited to tumors diagnosed in the tumor registry catchment area between January 1, 1958, and December 31, 1995, among persons in Hiroshima or Nagasaki at the time of the atomic bombings for whom DS86 dose estimates can be computed. With the use of these criteria, 146 tumors were excluded because 27 cases occurred in cohort members outside the study period, 73 tumors occurred in cohort members not in Hiroshima or Nagasaki at the time of the bombings, 11 tumors occurred in cohort members who lived outside the tumor registry catchment area at the time of diagnosis, and 35 tumors occurred in cohort members who do not have DS86 dose estimates. Because treatment for the first primary tumor could cause a subsequent tumor and because close medical surveillance might increase the chance of diagnosing a subsequent tumor, we excluded 58 nervous system tumors diagnosed after one or more earlier primary tumors. Seven of the exclusions involved simultaneous nervous system tumors, including three people with two primary meningiomas, one person with two schwannomas, two people with a meningioma (taken as the first primary) and a schwannoma, and one person with both an astrocytoma (taken as the first primary) and a cavernous hemangioma.

After these restrictions and exclusions, 228 first primary tumors of the brain or other parts of the nervous system, 35 tumors of the pituitary gland and adjacent areas (sellar region), and no tumors of the pineal gland were identified among the LSS members (Tables 1 and 2). Of the 263 tumors, 169 occurred among women and 94 occurred among men. The most frequent tumor types were meningioma (88 tumors) and schwannoma (55 tumors). There were also 43 gliomas (including astrocytomas), 15 other nervous system tumors of known type, 27 other nervous system tumors for which the available information was not adequate to histologically classify the tumor, and 35 pituitary gland tumors. The meningiomas were largely calvarial (69 cases, 78%). There were only three malignant meningiomas, all of which were calvarial. More than half the schwannomas were cranial (33 cases, 60%), generally occurring in the acoustic nerve (27 cases). The majority of gliomas were glioblastomatous (24 cases, 56%) or astrocytic tumors (14 cases, 33%). Tumors of the sellar region included 34 pituitary adenomas and one craniopharyngioma.

Many of the tumors diagnosed before 1978 were identified through the RERF autopsy program, which was active from the late 1950s through 1977. Indeed, 55% (70/128) of the tumors were diagnosed on the basis of autopsies before 1978 compared with only 4% (6/135) of the tumors diagnosed after 1977. Approximately 20% of the malignant tumors and 35% of the benign tumors were diagnosed at autopsy. In addition, 36% of the meningiomas and 49% of the pituitary gland tumors were diagnosed at autopsy. Variation in the proportion of autopsy-detected tumors with radiation dose was not statistically significant ($P = .3$). The number of clinically unapparent tumors was greatly reduced after the end of the autopsy program.

In the analyses of incidence, we first examined crude nervous system tumor incidence rates stratified by sex and radiation dose category (Table 2). The most striking suggestion of a dose response was seen for schwannoma, but the crude rates also suggest an increasing dose–response relationship for other tumor types. The dose–response relationships were more evident for tumors among men than among women. After modeling the baseline rates using the full dataset with allowance for radiation effects, the age-adjusted baseline rates for meningioma were almost three times higher for women than for men (female-to-male ratio = 2.6, 95% CI = 1.5 to 4.9), but for all other tumors combined, age-adjusted baseline rates for women were only about 65% of those for men (95% CI = 46% to 90%).

When the radiation effect was assumed to be linear in dose, the estimated ERR per Sv (ERR_{Sv}) was statistically significantly

Table 2. Sex-specific crude incidence rates* by dose group for various tumor types in Life Span Study subjects

	Weighted brain dose (Sv)†					Total No. of cases	No. of autopsy cases‡
	<0.005	0.005–0.099	0.10–0.49	0.50–0.99	⩾1.00		
Male							
Nervous system							
Glioma	2.9	1.8	2.0	3.4	10.9	20	6
Meningioma	1.6	1.8	1.0	3.4	7.2	14	4
Schwannoma	2.3	0.7	4.0	13.6	21.7	23	8
Other and NOS	2.6	2.5	2.0	3.4	10.9	21	3
Pituitary	1.0	3.5	1.0	6.8	0	16	11
Person-years§	306 178	281 956	100 016	29 378	27 629	745 157	
Female							
Nervous system							
Glioma	2.2	1.7	1.7	1.9	0	23	3
Meningioma	6.0	5.1	7.2	7.8	7.7	74	28
Schwannoma	2.2	1.7	3.9	5.8	7.7	32	5
Other and NOS	1.0	2.3	2.8	0	0	21	2
Pituitary	0.6	1.9	2.2	0	7.7	19	6
Person-years§	498 840	473 786	180 940	51 383	39 191	1 244 140	

*Cases per 100,000 person-years. NOS = not otherwise specified.

†Weighted doses were used to allow for greater biologic effectiveness of neutron doses. Individual weighted brain doses were calculated as the sum of the γ-ray dose plus 10 times the neutron dose using the DS86 system *(24,25)* and are expressed in sieverts (Sv).

‡Cases identified only at autopsy.

§Migration-adjusted person-years.

greater than zero for all nervous system tumors combined (ERR_{Sv} = 1.2, 95% CI = 0.6 to 2.1) (Table 3). Although the largest ERR_{Sv} estimate was observed for schwannomas (ERR_{Sv} = 4.5, 95% CI = 1.9 to 9.2), the ERR_{Sv} for all nervous system tumors other than schwannomas was also increased (ERR_{Sv} = 0.6, 95% CI = 0.1 to 1.4). Glioma (ERR_{Sv} = 0.6, 95% CI = –0.2 to 2.0), meningioma (ERR_{Sv} = 0.6, 95% CI = –0.01 to 1.8), and other or unspecified neural tumors (ERR_{Sv} = 0.5, 95% CI = <–0.2 to 2.2) all had similar ERR_{Sv} estimates, but the excess risk was not statistically significant for any of these diagnostic groups. These risk estimates indicate that, of the 228 nervous system tumors, about 32 (95% CI = 18 to 46), or 14%, were related to the radiation exposure. Schwannoma accounted for about two thirds of the excess (20 excess cases, 95% CI = 12 to 28). The estimated risk for pituitary gland tumors (ERR_{Sv} = 1.0, 95% CI = –0.1 to 3.1), although not statistically significant, was somewhat larger than that for non-schwannoma nervous system tumors. About four (95% CI = –0.8 to 10) of the 34 pituitary tumors were estimated to be related to radiation exposure.

To investigate the impact of the autopsy-only cases on the risk estimates, we reanalyzed the data after excluding the 75 tumors diagnosed only at autopsy (Table 3). The ERR_{Sv} estimates slightly increased after excluding these tumors, but the results did not differ substantially from those described above. For pituitary tumors, about half of which were detected at autopsy, the ERR_{Sv} also was larger among the clinically diagnosed than among the autopsy-only cases. These findings indicate that inclusion of the autopsy-only cases did not lead to any serious bias in the radiation risk estimates.

We investigated the adequacy of the linear dose–response model by considering various alternative descriptions of the dose response. Fig. 1 presents linear (solid line), nonparametric (points), and smoothed nonparametric (thick dashed line) *(35)* dose–response functions for schwannoma and for nervous system tumors other than schwannoma. The thin dashed lines indicate the uncertainty (± one standard error) in the nonparametric smoothed dose response. There is very good agreement between the linear fit and the smoothed data for nervous system tumors other than schwannoma, suggesting that the linear dose–response model describes these data quite well. For schwannoma, the relatively low but poorly estimated risk at very high doses tended to reduce the apparent linear low-dose slope and had an even stronger influence on the smoothed dose–response function. More formally, consideration of linear quadratic dose–response models provided little evidence of a statistically significant lack of fit of the linear dose–response model for schwannoma (P = .09) and no indication of a significant lack of fit for other nervous system (P>.5) tumors. For both groups, the linear model appears to provide a good description of the low-dose (e.g., <1 Sv) risks. For nervous system tumors as a group (P = .01) and for schwannoma (P<.001), the dose response was statistically significant when the analyses were carried out using only cohort members with doses of less than 1 Sv. In neither of these groups, nor for nervous system tumors other than schwannoma, was there any evidence of statistically significant differences in the slope over this low-dose range and that over the full-dose range. Taken together, these findings suggest that the LSS data are consistent with a linear dose response for doses ranging from zero to two or more Sv.

We next performed tests for heterogeneity or trends in the radiation effect with regard to sex, age at exposure, and attained age for schwannoma, other nervous system tumors (excluding schwannoma), and meningioma (Table 4). Because of the small number of excess tumors, precise characterization of effect modification (i.e., how the radiation-associated excess risks vary with factors such as sex, age at exposure, or attained age) is not possible for these data. However, we did note some potentially interesting patterns. The ERR_{Sv} for men was statistically significantly higher than that for women for nervous system tumors other than schwannoma (P = .05), with a male-to-female ERR_{Sv} ratio of 14. There also was a weak, albeit not statistically significant, suggestion of an age-at-exposure effect for nervous system tumors other than schwannoma (P_{trend} = .06), with people exposed to the atomic bomb radiation before age 20 having larger estimated risks (ERR_{Sv} = 1.2, 95% CI = 0.3 to 2.9) than people exposed after age 20 (ERR_{Sv} = 0.2, 95% CI = <–0.2 to 1.0). There was no evidence (P_{trend} = .5) that the ERR for nervous system tumors other than schwannoma varied with attained age, suggesting that the elevated risks may persist throughout lifetime for exposed individuals. A similar pattern was observed when meningioma was considered separately, with ERR_{Sv} estimates for those exposed before and after age 20 of 1.3 (95% CI = –0.05 to 4.3) and 0.4 (95% CI = <–0.1 to 1.7), respectively. We also tested for time-since-exposure effects on the ERR (data not shown). There was no indication of statistically significant effects for schwannoma (P>.5) or for nervous system tumors other than schwannoma (P = .09).

Table 3. Fitted linear excess relative risk estimates by tumor type for all cases (autopsy and nonautopsy) and excluding autopsy-only cases* in Life Span Study subjects

	Nervous system	Glioma and astrocytoma	Meningioma	Schwannoma	Other nervous system†	Pituitary
			All cases			
Excess RR per Sv (95% CI)	1.2 (0.6 to 2.1)	0.56 (–0.2 to 2.0)	0.64 (–0.01 to 1.8)	4.5 (1.9 to 9.2)	0.51 (<–0.2 to 2.2)	0.98 (<–0.2 to 3.5)
No. of cases	228	43	88	55	42	35
No. of excess cases	31.7	3.1	6.8	20.3	2.8	3.7
			Excluding autopsy-only cases			
Excess RR per Sv (95% CI)	1.4 (0.6 to 2.5)	0.60 (<–0.2 to 2.4)	0.82 (–0.1 to 2.6)	4.6 (1.5 to 10)	0.75 (<–0.2 to 2.8)	1.5 (<–0.2 to 6.7)
No. of cases	169	34	56	42	37	18
No. of excess cases	26.9	2.6	5.9	15.7	3.6	3.1

*Maximum likelihood estimates from a linear dose–response model with adjustment for age, birth corhort, period, and sex effects on the background rates; CI = confidence interval; RR = relative risk; Sv = sievert.

†This category includes 27 tumors of unknown histology and 15 of known histology.

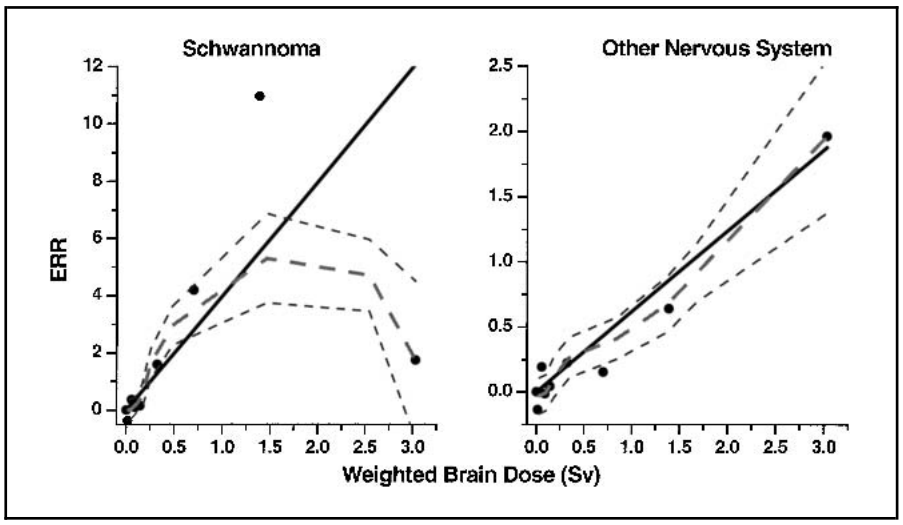

Fig. 1. Nervous system tumor dose–response functions. The plots present smoothed and nonparametric estimates of the dose–response functions for schwannoma and other nervous system tumors. The **points** are nonparametric estimates of the excess relative risk (ERR) in various dose categories. The **solid lines** show the fitted linear dose response (sex-averaged for schwannoma). The **thick dashed line** is a simple smoothed version of the nonparametric estimates *(32).* The **thin dashed lines** are one-standard-error bounds for the nonparametric smoothed curves.

Table 4. Parameter estimates (excess relative risk [RR] and 95% confidence intervals [CIs]) and hypothesis tests for the effect modification* in Life Span Study subjects

	Schwannoma	Nervous system tumors excluding schwannoma	Meningioma
Sex			
Male	8.0 (2.7 to 21)	1.4 (0.4 to 3.3)	1.6 (−0.04 to 7.1)
Female	2.3 (0.3 to 7.0)	0.1 (−0.2 to 0.9)	0.4 (−0.2 to 1.7)
P for difference	.12	.05	.4
Age at exposure, y†			
Excess RR per sievert for survivors exposed at 30 years of age	4.2 (0.9 to 8.9)	0.15 (0.0 to 1.0)	0.5 (<0 to 1.8)
Change per decade, %	−12 (−60 to 32)	−62 (−95 to 4)	−38 (−95 to 60)
P_{trend}	>.5	.06	.3
<20	6.0 (2.1 to 14)	1.2 (0.3 to 2.9)	1.3 (0.01 to 4.5)
20–39	2.6 (<−0.2 to 10)	0.3 (<−0.2 to 1.6)	0.5 (−0.05 to 2.8)
⩾40	3.3 (0.33 to 11)	0.1 (<−0.2 to 1.2)	0.3 (<−0.1 to 2.0)
P for heterogeneity‡	.3	.25	>.5
Attained age, y§			
Excess RR per sievert at age 60	3.6 (0.8 to 8.2)	0.6 (0.08 to 1.3)	0.6 (<0 to 2.3)
Change per decade, %	−35 (−74 to 9)	−28 (−95 to 100)	−54 (−95 to 130)
P_{trend}	.11	.5	.12
<50	8.4 (2.7 to 22)	0.6 (<−0.1 to 1.3)	2.0 (−0.1 to 12)
50–69	3.0 (0.4 to 8.7)	0.6 (−0.2 to 1.8)	0.5 (<−0.1 to 2.2)
⩾70	3.0 (0.2 to 10)	0.8 (−0.1 to 2.7)	0.7 (<−0.1 to 2.4)
P for heterogeneity‖	.3	.5	>.5

*Maximum likelihood estimates in an excess relative risk model with adjustment for city, sex, age, birth cohort, and period effects on background rates. Two-sided *P* values and confidence intervals are based on likelihood ratio tests *(33,34).* CI = confidence interval.

†Two-sided *P* value for testing the hypothesis that the excess RR exhibits a log-linear trend with age at exposure. The excess RR is given for a reference age at exposure of 30. The effect of interest is expressed as the percentage change in the excess RR per decade increase in age at exposure. Thus, for schwannoma, the estimated risks for people exposed at ages 20 and 40 are 4.7 (= 4.2 × [1 + 0.12]) and 3.7 (= 4.2 × [1 − 0.12]), respectively.

‡Two-sided *P* value for testing the hypothesis that the excess RR varies with age at exposure. The parameters are excess RR per sievert estimates for the indicated age at exposure groups.

§Two-sided *P* value for testing the hypothesis that the excess RR exhibits a log-linear trend with attained age (age for diagnosis). The excess RR is given for a reference age of 60. The effect of interest is expressed as the percentage change in the excess RR per decade increase in attained age. Thus, for schwannoma, the estimated risks for ages 50 and 70 (assuming exposure prior to the age of interest) are 4.9 (= 3.6 × [1 + 0.35]) and 2.3 (= 3.6 × [1 − 0.35]), respectively.

‖Two-sided *P* value for testing the hypothesis that the excess RR varies with attained age. The parameters are excess RR per sievert estimates for the indicated age groups.

With only four excess pituitary tumors, it is not possible to make meaningful inferences about variations in the excess pituitary tumor risks with age at exposure or time. Evaluation of the effect of sex also is limited by the number of cases. However, the estimated ERR_{Sv} for women was considerably greater than that for males ($P = .13$). For women, the pituitary ERR_{Sv} estimate was 2.0 (95% CI = –0.1 to 8.9). For men, the best estimate of the ERR_{Sv} was negative, resulting from a smaller-than-expected number of cases in the highest dose group. However, this apparent reduced risk is not statistically significant ($P>.5$, with an upper 95% confidence bound of 2.2).

Because inclusion of the autopsy-only cases could bias estimates of effect modification, particularly in terms of age and time, we also assessed effect modification excluding these cases. There were no marked changes in the parameter estimates or conclusions about the statistical significance of these effects.

We also examined EARs for schwannoma, nervous system tumors other than schwannoma, and meningioma (Table 5). Al-

Table 5. Excess absolute rate estimates by nervous system tumor type in subjects from the Life Span Study

Tumor type	Excess cases per 10 000 person-year Sv* (95% CI)	Attained-age P_{trend} (% increase per decade)
Schwannoma	0.67 (0.3 to 1.1)	>.5 (3)
Nervous system, excluding schwannoma	0.28 (−0.03 to 0.7)	.3 (30)
Meningioma	0.14 (0.00 to 0.45)	.5 (20)

*In age-dependent models, these estimates are roughly equal to the (sex-averaged) excess absolute rate estimates at age 60. Sv = sievert; CI = confidence interval.

though there was no evidence of statistically significant variation in the excess rates with attained age, the point estimates of the change in the EAR per decade are relatively large for nervous system tumors other than schwannoma and meningioma separately. Similar to the ERR estimates, there was a suggestion that the EAR is greater for men than for women. This difference approaches statistical significance for schwannoma ($P = .08$) and for nervous system tumors other than schwannoma ($P = .06$), but not for meningioma considered separately ($P > .5$).

Discussion

The etiology of brain and nervous system tumors is not well understood. One of the few environmental agents causally linked to these tumors is cranial radiotherapy during childhood *(3).* However, data are sparse and the association has not been adequately quantified. Increased risks of primary nervous system tumors, largely benign, have been demonstrated following cranial radiation exposure (typically exposures in excess of 1 Gy) from childhood radiotherapy for benign head and neck diseases *(4–7,9).* Increased incidence of subsequent nervous system tumors also has been observed in childhood cancer patients who received extremely high-dose (often in excess of 10 Gy) cranial radiotherapy *(8,10–12).* The current study adds unique information on the tumorigenic effects of radiation exposure at doses below 1 Gy to the adult nervous system later in life and about the relative radiosensitivity of different nervous system tissues and organs.

Although our data show a statistically significant increased risk of all nervous system tumors combined, the risk was substantially higher for schwannoma than for any other nervous system tumor type. When considered individually, risks for glioma, meningioma, or other non-schwannoma nervous system tumors were not found to exhibit statistically significant radiation-related increases in risk. However, because the ERR estimates were elevated for each histologic type, analyses of all non-schwannoma nervous system tumors combined demonstrated a statistically significant radiation effect.

An enhanced risk of glioma has been seen following moderate-dose radiotherapy for tinea capitis *(5,6),* and large risks of gliomas have been reported following very high radiation doses, e.g., after prophylactic radiation therapy in childhood for acute lymphoblastic leukemia *(11,12)* or after radiation therapy for pituitary tumors *(36).* In some studies, excess relative risks were greater for schwannoma than for other nervous system tumors *(5,6,12).* Our results are generally consistent with these observations.

To date, most reports of radiation-associated nervous system tumors have been based on childhood exposures. The LSS is unique in that it permits direct assessment of how radiation effects on nervous system tumor incidence vary over a large range of ages at exposure. This study has several additional strengths. LSS cohort members have individually estimated organ doses. Tumor incidence could be ascertained on the basis of data from population-based tumor and tissue registries, with final pathology review carried out on the basis of consistently applied, modern diagnostic criteria. The fact that 20% of the benign tumors in this study were identified at autopsy is also a potential strength of the study because inclusion of these cases increases the ability of the study to characterize radiation effects. Although the use of these cases raises concerns about potential biases in the radiation risk estimates resulting from dose-related ascertainment rate differences, our analyses suggested that after allowing for temporal variation in autopsy rates, there are no indications of bias in the radiation risk estimates.

Our results for nervous system tumors other than schwannoma and for meningioma considered separately are consistent with a marked decrease in the ERR_{Sv} with increasing age at exposure, but the effect is not statistically significant, possibly because of the relatively small number of radiation-associated cases in this population. The lack of a statistically significant attained-age effect on the radiation risks for nervous system tumor incidence may also reflect these limitations of the data. However, the age-group-specific point estimates of the ERR_{Sv} do not suggest a consistent pattern of change with increasing age, and statistically significant attained-age effects have not been reported in other studies.

Although the evidence for sex differences in excess relative risks was not strong, men generally had higher excess relative risks than women, even for meningioma, for which background rates are considerably greater for women than for men. In one population-based incidence study, meningioma rates increase with age, are about two times higher among women than among men, and typically account for about 20% of intracranial tumors *(37).* In the LSS data, background meningioma incidence rates increased with age, women had about three times the incidence of men, and meningioma comprised almost 50% of the nervous system tumors, mostly because of the large number of meningiomas detected at autopsy. The background sex difference was reduced, but not eliminated, when analyses were restricted to meningiomas not discovered at autopsy. Although the sex difference in the ERR_{Sv} for meningioma in this cohort was not statistically significant ($P = .4$), the point estimate of the sex ratio (female-to-male ratio = 0.3) of the excess relative risks is consistent with observations from another study *(38),* in which it was noted that men have somewhat greater age-specific rates of meningioma than women.

The mechanisms of tumorigenesis in the human brain are believed to be different than those in other tissues and organs because the brain is well protected, not exposed to many exogenous agents, and only glial cells (probably astrocytes) proliferate after puberty *(39).* Inskip et al. *(3)* have suggested that traumatic injury to the brain increases cell proliferation or breakdown of the blood–brain barrier, thus increasing the risk of brain tumor development.

Preston-Martin et al. *(40)* also suggested that head trauma may be an important risk factor for meningioma. It is possible that increased cell proliferation or breakdown of the blood–brain

barrier resulting from head injury during the atomic bombings enhanced the tumorigenic effects of radiation exposure. Because benign tumors frequently occur outside the brain and the protection of the blood–brain barrier, they may be more susceptible to radiation damage. Even though there is a positive association between non-radiation-related injury and radiation dose among the LSS survivors, the effects of head trauma are unlikely to fully explain the radiation dose response because the risk of physical trauma was also quite high for many survivors who received little or no radiation dose. If trauma was playing a major role in the dose response, we would expect the incidence of nervous system tumors among the 15 600 proximal survivors (i.e., within 3 km) with low radiation exposure (<5 mSv) to be greater than that for the 23 500 more distal survivors with similar low radiation exposure but much less trauma. In fact, such differences were not observed for all nervous system tumors as a group, for schwannomas, or for meningiomas when considered separately. Our results support those of Ron et al. *(5),* who noted large radiation-associated risks for schwannomas in the Israeli tinea capitis study in which trauma is not a risk factor. Thus, it is unlikely that the effects of physical trauma in the atomic bomb survivors are seriously confounding or biasing the radiation risk estimates.

This study indicates that relatively low-dose radiation exposure plays a role in the etiology of nervous system and pituitary tumors, with a weak indication of somewhat higher relative risks for those exposed during childhood. Although most of the tumors were benign, radiation-induced meningiomas reportedly have more atypical or anaplastic histology than spontaneous meningiomas and have a high rate of recurrence *(41–43).* Among the LSS cases, there were three anaplastic and one atypical meningioma (two in cohort members with zero dose and two in cohort members with doses of about 1 Sv), making it difficult to draw any firm conclusion regarding radiation-induced meningioma.

New uses of medical irradiation involving exposure of the central nervous system have heightened interest in radiation effects on nervous system cancer risks. The use of radiation treatment for benign diseases of the nervous system, such as for intracranial arteriovenous malformation *(44),* can result in high doses to parts of the brain. In addition, the use of pediatric computed tomography (CT) scans *(45),* including brain scans, has increased dramatically over the last decade. It has been predicted *(46)* that the rapid rise in the use of CT scans will lead to increases in the lifetime risk of cancers of the brain and other tissue. Although additional follow-up of the LSS cohort and other exposed populations will be necessary to fully quantify the lifetime risks for nervous system tumors, our findings demonstrate that radiation exposure can increase the risk of nervous system tumors and suggest that these increased risks persist throughout lifetime, regardless of the age at exposure.

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NOTES

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